PERSPECTIVE

Diabetes and CVD: medication warnings

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Patients with both cardiovascular disease (CVD) and type 2 diabetes take medications for their CVD, their diabetes and a range of other comorbidities, and there is a great potential for dangerous medical side effects and interactions. The more serious adverse effects of oral hypoglycaemic agents are discussed.

Key points

- **Diabetes and cardiovascular disease frequently co-exist and GPs and specialists involved in cardiovascular and diabetes medicine need to be aware of the possible serious medication side effects of oral hypoglycaemic agents and interactions between them and other drugs the patient may be taking.**
- **The general 'red flags' for medication problems include renal impairment, patient frailty and polypharmacy/nonadherence.**
- **Metformin may have the serious side effect of lactic acidosis, and indicators of this include cardiac or pulmonary failure, shock and vitamin B_1 deficiency.**
- **Sulfonylureas may be associated with severe hypoglycaemia, especially in patients who have a past history of hypoglycaemia, have neuropathy and live alone.**
- **Glitazones use may result in cardiac failure. A history of cardiac failure, oedema, diuretic use and use of NSAIDs or insulin should raise suspicion of this.**

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Diabetes and cardiovascular disease (CVD) frequently coexist. Professionals involved in cardiovascular medicine need to be aware of the frequency and importance of type 2 diabetes in patients with CVD, and professionals involved in diabetes care need to be aware of the frequency and importance of CVD in those with type 2 diabetes.

Patients with both CVD and type 2 diabetes take medications for their CVD, their diabetes and a range of other comorbidities, and possibly also multiple complementary medicines. Current medications may be stopped or the dose changed, new medications may be added and patients may make mistakes. There is, therefore, a great potential for dangerous medical side effects and interactions.

This article presents hypothetical case studies in one patient that illustrate some of the potentially lethal side effects of the major hypoglycaemic medications used in type 2 diabetes and identify the 'red flags' indicating the patients in whom these side effects are particularly likely.

Disasters waiting to happen

Case scenario

Pauline is 73 years old and has had type 2 diabetes for 18 years. Diabetes 'runs in the family', with her mother and three of her five siblings having had diabetes diagnosed in their 50s or 60s. Being overweight also runs in the family and Pauline herself is 151 cm tall and weighs 73.2 kg (BMI, 32.1 kg/m^2). She lives on her own in a unit, but her two daughters live close by and call in regularly.

Pauline's diabetes had been moderately controlled until four years ago when her glycosylated haemoglobin (HbA_{1c}) started increasing from 7.4% (57.4 mmol/mol) to its current level of 8.9% (73.8 mmol/mol) despite maximal doses of oral hypoglycaemic agents (metformin 1000 mg twice daily, glibenclamide 20 mg per day and pioglitazone 45 mg per day). Pauline has finally agreed to start insulin.

Pauline has had laser therapy for diabetic retinopathy, has evidence of peripheral neuropathy with loss of sensation below her ankles, a plasma creatinine level of 120 µmol/L (normal range, 50 to 120 µmol/L) and an estimated glomerular filtration rate (eGFR) of 55 mL/min/1.73 m^2. Four years ago she had a stroke, which affected her right arm, but she made a good functional recovery. Her ECG showed evidence of an inferior myocardial infarction but she had no history of symptomatic coronary heart disease. Pauline also takes a combined angiotensin receptor antagonist–thiazide–amlodipine hypotensive, a statin, a proton pump inhibitor and an NSAID, as well as vitamin supplements and various health foods.

Potential problems

The commonly used oral hypoglycaemic agents metformin, the sulfonylureas and the glitazones have side effects that are common and of considerable nuisance value and also some that are potentially lethal (Table 1).[1] Neither Pauline, her daughters nor her GP realise that she is at high risk of three of these potentially lethal side effects of diabetes medications, that is lactic acidosis, severe hypoglycaemia and cardiac failure (Table 1).

Pauline also has two of the general 'red flags' for medication problems: she has renal impairment and she is taking many medications (Table 2).[1] Serious medication side effects are often associated with a combination of general risk factors for medication problems as well as one or more risk factors specific for the particular oral hypoglycaemic agent (e.g. renal impairment and hypoxia predisposing to lactic acidosis with metformin). These combinations are dual, triple and sometimes quadruple 'whammies'.

Table 1. Oral hypoglycaemic agents: side effects[1]*

Oral hypoglycaemic agent	Nuisance side effect	Potentially lethal side effect
Metformin	Gastrointestinal disturbance	Lactic acidosis
Sulfonylureas	Weight gain	Severe hypoglycaemia
Glitazones	Oedema Weight gain	Cardiac failure

*The less commonly used oral hypoglycaemic agents are not included.

Table 2. Red flags for medication problems[1]

Medication	Medication problem	Red flags for problem
General medication use	Medication accumulation	Renal impairment
	Minor problems potentially becoming major problems	Patient frailty*
	Increased likelihood of adverse effects	Polypharmacy Nonadherence
Oral hypoglycaemic agents		
Metformin	Lactic acidosis	Cardiac or pulmonary failure Shock Vitamin B_1 deficiency
Sulfonylureas	Hypoglycaemia[3]	Past history of hypoglycaemia Neuropathy Living alone
Glitazones	Cardiac failure	Past history of cardiac failure Oedema/diuretic use NSAIDs/insulin use

Note: Serious medication side effects are frequently associated with a combination of general risk factors for medication problems as well as one or more risk factors specific for the particular oral hypoglycaemic agent.

* Patient frailty = biological age older than 85 years.

Potential disaster number 1

Case scenario

Pauline woke at 2 a.m. because of shortness of breath, which rapidly worsened. She triggered her Medic-Alert system, an ambulance took her to hospital and she was admitted to the intensive care unit.

Her electrolytes, renal function and blood gases were grossly abnormal.

- *Electrolytes and renal function:*
  - *sodium, 138 mmol/L (normal range, 137 to 145 mmol/L)*
  - *potassium, 6.2 mmol/L (3.1 to 4.2 mmol/L)*
  - *chloride, 105 mmol/L (100 to 109 mmol/L)*
  - *bicarbonate, 7 mmol/L (24 to 32 mmol/L)*

  - *anion gap, 32.3 mEq/L (8 to 5 mEq/L); this was later identified as lactic acidosis*
  - *urea, 12.2 mmol/L (3 to 8 mmol/L)*
  - *creatinine, 162 µmol/L (50 to 120 µmol/L)*
- *Arterial blood gases, using oxygen mask:*
  - *PO_2, 120 mmHg*
  - *PCO_2, 25 mmHg (35 to 45 mmHg)*
  - *pH, 7.1 (7.35 to 7.45)*

At 4.15 a.m. she had a cardiac arrest and despite efforts at resuscitation was pronounced dead at 4.50 a.m.

Case discussion

Metformin can cause gastrointestinal disturbance (nausea, gastric irritation, diarrhoea and flatulence), which fortunately usually decreases over time and is not so severe that the patient stops taking metformin. Rarely, metformin is associated with lactic acidosis, usually in association with a comorbidity or an event that precipitates the vicious cycle of lactic acid accumulation, impaired cardiac function/arrhythmia, hypoxia and further lactic acid accumulation.[2]

As noted, Pauline had two of the general 'red flags' for medication problems: renal impairment and polypharmacy (Table 2).[1] She may also have had one or more of the specific risks for lactic acidosis: cardiac failure precipitated by another atypical myocardial infarction or vitamin B_1 deficiency associated with the 'tea and toast' diet of older people living on their own.

In retrospect, Pauline's metformin dose was excessive, given her renal impairment, particularly as she had a much smaller lean body mass than her weight implied (see the box on this page). She had already had a myocardial infarction, which may well have impaired her myocardial function, and she may also have had the cardiomyopathy that is associated with type 2 diabetes, especially in those with a BMI greater than 30 kg/m^2. The combination of an accumulation of metformin associated with the high dose and renal impairment and myocardial dysfunction causing hypoxia was enough to trigger the vicious cycle that led to her death.

Pauline's renal function

Pauline was on a large dose of metformin (2 g per day) but her weight (73.2 kg), her normal plasma creatinine level (120 µmol/L) and an eGFR of 55 mL/min/1.73 m^2 may have reassured her GP that the dose was not excessive. In fact, both her real GFR and her lean body mass were much lower, as explained below.

As a rough rule: healthy weight (kg) = height (cm) – 100 (see note below)

For Pauline = 151 – 100 = 51 kg (not 73.2 kg).

The formula to calculate eGFR includes age, sex and plasma creatinine level as this information is available to the laboratory generating the report.[6] However, the formula does not apply to populations of non-European origin, does not allow for body size and can give misleading results at extremes of body mass (as in Pauline's case).

In patients not covered by the eGFR formula, it is recommended that the Cockcroft-Gault equation be used to adjust doses of medication. A simplified version of the Cockcroft-Gault equation for creatinine clearance (mL/min) in women is:

[140 – age in years] x [healthy body weight in kg] ÷ P-creat (µmol/L)*

For Pauline = 67 x 51 ÷ 120 = 28 mL/min.

It is recommended that metformin not be used or that the dose be limited to 500 mg/day in patients with a reduced GFR.

Note. Healthy body weight corresponds to BMI of 18.5 to 25 kg/m^2. The relation between height and healthy weight has been derived empirically by the author and is approximately correct between heights of 1.4 and 2.0 m. Pauline's BMI is 32.1 kg/m^2, but at a healthy body weight of 51 kg it would be 22.4 kg/m^2, so her excess body fat is 22.2 kg (73.2 – 51).

* Multiply by 1.25 for men to allow for their higher proportion of lean body mass as compared with women.

Potential disaster number 2

Case scenario

Pauline was found wandering in the street not far from her unit. She had no idea how she got there or where she lived. Her daughter's address was found in her handbag and she was contacted. Her daughter checked Pauline's blood glucose level, which was 2.1 mmol/L. At the hospital, her ECG showed atrial fibrillation, widening of the QRS, ST depression and T-wave inversion in all leads, as well as the previous ECG changes of her inferior myocardial infarction.

After 36 hours in the intensive care unit with cardiac monitoring, Pauline was transferred to the ward but remained confused for a further 24 hours. She was later started on gliclazide and transferred home.

Case discussion

Pauline may have been chronically hypoglycaemic for some time, forgetting things or being confused more often than usual, and yet have been able to remain at home and interact with outsiders. Her family may have thought she was just getting more forgetful, or showing the early signs of dementia. Hypoglycaemia can present insidiously in this way, as well as dramatically with loss of consciousness or fitting.[3]

As noted, Pauline had two of the general 'red flags' for medication problems. She had excess fatty tissue (22.2 kg, or 30% of her body weight) and a small fat-free body mass (see the box on this page). She was taking a large dose of a sulfonylurea (glibenclamide 20 mg per day), and her renal impairment would have reduced the clearance of this drug and its active metabolites, so she may have had very high levels of active sulfonylurea circulating. This is why glibenclamide and the other long-acting sulfonylurea, glimepiride, are not recommended in patients with renal impairment.

Hypoglycaemia and Pauline's ECG[4]

Severe hypoglycaemia has long been noted to cause ECG changes. In the 1930s, severe hypoglycaemia was induced therapeutically to treat mental disorders (schizophrenia and depression). Less severe hypoglycaemia was also induced to assess gastric acid secretion before surgical vagotomy for peptic ulcer disease, and is still occasionally used to evaluate hypothalamic pituitary function.

The changes noted in the 1930s included arrhythmias (sinus bradycardia and tachycardia, atrial fibrillation), minor changes in the P wave and QRS complex, ST segment changes (depression and occasionally elevation) and flattening or inversion of the T wave, and these could persist for several months.

Potential causes for the changes include a mismatch between increased myocardial energy needs induced by the sympatho-adrenal activation and the limited availability of glucose, an intracellular potassium shift causing hypokalaemia, and cerebral dysfunction, all of which are associated with hypoglycaemia.

Pauline also had factors that specifically predisposed her to hypoglycaemia: neuropathy, which would impair her recognition of and response to hypoglycaemia, and her living alone, so there would be no-one with her who might recognise that she was acting strangely or find her if she became unconscious.

Pauline's response to hypoglycaemia would be further reduced because less glucose would be released (through gluconeogenesis) by the decreased kidney mass in response to hypoglycaemia. Pauline's responses would also be impaired by hypoglycaemia itself, which leads to a vicious cycle of hypoglycaemic unawareness causing ongoing and potentially more severe hypoglycaemia.

It is not commonly recognised that hypoglycaemia can be associated with ECG abnormalities and arrhythmias that may be fatal (see the box on this page).[4]

Potential disaster number 3

Case scenario

Pauline added insulin to her hypoglycaemic schedule as planned and the dose was titrated over the next four weeks from 10 units at bed time to 38 units daily. Pauline visited her GP because she was getting up several times at night to pass urine and thought this might have been caused by her diabetes. Urinalysis showed no glycosuria. Results of examination were similar to previous occasions except that she had possibly a little more ankle oedema. Her GP reassured her.

Later that week one of Pauline's daughters was seeing the same GP and mentioned that Pauline had been admitted to hospital with heart failure the day before.

Pauline's cardiac failure responded to more vigorous diuretic therapy and she returned to her unit and to her previous level of activity.

Diabetes, obesity and the heart[5]

Coronary heart disease

Type 2 diabetes is often associated with the other components of the metabolic syndrome, particularly central overweight, hypertension, dyslipidaemia and prothrombosis. These coronary risk factors can cause atherosclerotic disease of the major coronary arteries. The smaller, more peripheral, arteries can also be affected in type 2 diabetes, which can be associated with angina and myocardial dysfunction (the so-called cardiac syndrome X).

Cardiac failure with both systolic and diastolic dysfunction

Apart from coronary heart disease, the risk of heart failure in diabetes and obesity is thought to be associated with increased cardiac work, myocardial dysfunction associated with insulin resistance and myocardial steatosis ('fatty heart') and an increased risk of atrial flutter/fibrillation.

Case discussion

In retrospect, Pauline's nocturia was a warning symptom of increasing peripheral oedema, the excess fluid being reabsorbed from the extracellular space at night, while she was supine, and renally excreted.

Pauline was known to have coronary heart disease and had many of the risk factors predisposing to this and cardiac failure (see the box on this page).[5] She also had two of the general risk factors for medication side effects.

The sequence of events suggests that this disaster was precipitated by the addition and titration of insulin, with its sodium-retaining propensity, on top of Pauline's high dose of the glitazone and her NSAID, which also have sodium-retaining properties.

It is also possible that Pauline inadvertently or purposely stopped taking her antihypertensive medication (the angiotensin–amlodipine–thiazide combination). This would have increased her cardiac load and had a dual direct effect on her oedema (lesser peripheral vasodilation from stopping the amlodipine decreasing it, and lesser diuresis from stopping the thiazide increasing it). She may also have eaten food or taken health supplements with significant loads of sodium, or with ingredients that might increase cardiac work, blood pressure or heart rate.

The glitazones (pioglitazone and rosiglitazone) have the interesting but therapeutically awkward property of requiring several weeks after initiation before attaining their full effect and, conversely, of continuing to have their therapeutic and side effects for some time after cessation. As Pauline was starting insulin, the pioglitazone could have been stopped and the insulin titrated to achieve its desired therapeutic effect over several weeks, and the episode of cardiac failure may not have occurred. Fortunately, Pauline's cardiac failure responded to more vigorous diuretic therapy.

Summary

Diabetes and cardiovascular disease often coexist and professionals involved in cardiovascular and diabetes medicine need to be aware of the frequency and importance of this coexistence and the 'red flags' that indicate patients at high risk for potentially lethal side effects from oral hypoglycaemic agents.

The general 'red flags' for medication problems include renal impairment, patient frailty, polypharmacy/nonadherence. The 'red flags' for the potentially lethal side effects of specific oral hypoglycaemic agents are:

- lactic acidosis with metformin use: red flags are cardiac/pulmonary failure, shock and vitamin B_1 deficiency
- severe hypoglycaemia with sulfonylurea use: red flags are past history of hypoglycaemia, neuropathy and living alone
- cardiac failure with glitazone use: red flags are past history of cardiac failure, oedema, diuretic use and use of NSAIDs or insulin.

The serious side effects associated with the oral hypoglycaemic agents are frequently also associated with other factors that themselves increase the risk of the side effects (the so-called 'double, triple or quadruple whammies').

When considering the effect of renal impairment on medication dosing, the GFR should be calculated using the Cockcroft-Gault equation rather than by the eGFR equation, as it is more accurate. Hypoglycaemia can cause multiple abnormalities in the ECG, some of which may persist long after the hypoglycaemic episode. Diabetes and obesity have multiple adverse effects on the heart, including atherosclerosis of proximal and distal coronary arteries, increased cardiac work, myocardial dysfunction and increased risk of atrial flutter/fibrillation. **CT**

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